

A TUMOUR SYNDROME AFFECTING CHILDREN IN TROPICAL AFRICA

DENIS BURKITT, M.D., F.R.C.S.E.

Department of Surgery, Makerere College Medical School, and Mulago Hospital, Kampala, Uganda

WITH the exception of leukæmia, the vast majority of malignant tumours occurring in children consist of those developing in the central or autonomic nervous systems, the kidneys and the lymph glands (Campbell, Gainsford, Paterson and Steward, 1961). The metastases from these neoplasms are most frequently observed in the liver, the lungs and the skeleton, excluding the jaws.

Among the rarest of sites in which malignant tumours have been recorded in children might be listed the ovaries, the thyroid, the salivary glands, the testes, the extra-dural space in the spine, the orbit, excluding the eye, and, above all, the jaws. Yet it is in these very sites that tumour deposits are frequently observed in the tumour syndrome about to be described and discussed. Moreover, tumours are not only commonly found in one or other of these unusual sites, but many of these structures are frequently concomitantly involved in one patient.

To add to the bizarre behaviour of this tumour syndrome the lungs are usually spared in a cancer that might appear to be blood-disseminated, and lymph-node enlargement or splenic involvement is exceptional in what has been shown to be a lymphoid tumour.

These are but some of the peculiarities of this unusual and yet distinctive syndrome. The main clinical features have already been described (Burkitt, 1958; Burkitt and O'Connor, 1961; Burkitt and Davies, 1961) and a detailed description of the pathology has been published (O'Connor, 1961). Attention has been drawn to certain radiological aspects of the jaw tumours (Davies and Davies, 1960), to the unusual geographical distribution (Burkitt, 1958; Burkitt and O'Connor, 1961) and to the suggested significance of this limited distribution (Burkitt and Davies, 1961; Burkitt, 1962).

A brief review of the recorded observations on this tumour syndrome will be given before discussing its possible significance as a contribution to knowledge of cancer ætiology.

Incidence Relative to other Tumours

As has been pointed out already (Burkitt and

O'Connor, 1961), this tumour syndrome is not only the commonest cancer of children in certain parts of Africa, but in Uganda at least it accounts for more than the sum total of all other malignant tumours in children. During the last 10 years over 200 cases have been recorded in Uganda.

Age and Sex Incidence

There is no evidence that the tumour is more common in one sex than the other. The age incidence is characteristic. The tumour is almost unknown under the age of two years and is rare over the age of 14 years. There is a steep rise from the age of two to a maximum incidence at five, and then a gradual fall tailing off to 14.

Race Incidence

It is not a tumour of Africans, but is a tumour of children in Africa. Available evidence suggests that African children are no more susceptible than children of other races. Two of the first 150 patients recorded in Uganda were Indian children. This is as many as would have been expected in a population with 100 Africans to one Indian. The tumour has also been seen in a child with a European father and Eurasian mother, and one of four cases reported to me from the Sudan was a Syrian boy. A tumour apparently of the same nature occurred in the child of American missionaries in the Congo (Williams, 1961).

Clinical Features

A Jaw Tumour

The most characteristic presentation is a tumour involving the jaws (Fig. 1). The first evidence of this tumour is loosening of the molar teeth, and these cases are often seen first by a dental surgeon. Curiously, the lesion always starts at one side of the jaw and never near the midline. A soft swelling soon appears at either side of the alveolus, and as the tumour grows rapidly the teeth become displaced and eventually fall out (Fig. 2). The tumour does not ulcerate through the skin or mucosa except at the site of empty tooth sockets.

In a high proportion of patients two or more quadrants of the jaws are involved simultaneously,

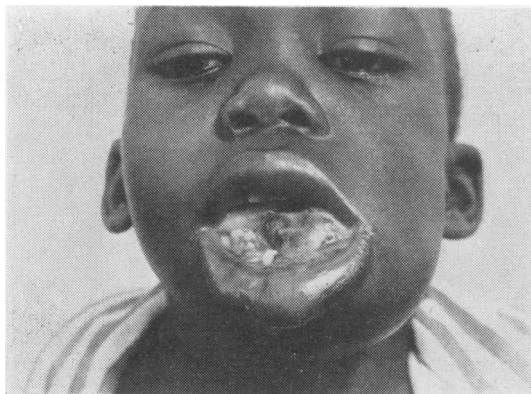


FIG. 1.—Tumour in the left mandible in a boy aged three years.

and not infrequently all four quadrants are involved without any demonstrable continuity of tumour between each lesion. When more than one jaw quadrant is involved it is nearly always the maxilla and mandible on the same side or all four quadrants. Only once has a bilateral maxillary tumour without demonstrable mandibular involvement been observed, and no case of bilateral mandibular tumour has yet been seen except in the presence of concomitant bilateral maxillary tumours.

There is usually no clinical enlargement of cervical lymph nodes even in the terminal stages of the lesion.

An Orbital Tumour

Children commonly present with exophthalmos (Fig. 3) and chemosis. These cases are consequently often first seen in the eye department. The tumour invading the orbit and displacing the eye is believed to originate in the upper part of the maxilla. As the tumour progresses the exophthalmos becomes associated with the oral involvement described above. Similarly, in the later stages of tumours starting apparently in relation to the upper teeth exophthalmos frequently ensues. This tumour is distinguishable from retinoblastoma in that the eye itself is not involved until the late stages. The tumour, however, when far advanced, is clinically, and usually histologically, indistinguishable from advanced retinoblastoma (Fig. 4). Exophthalmos is believed to be but one mode of presentation of a maxillary tumour.

An Abdominal Tumour

In recorded cases this is the next most common presentation to the jaw tumour (Fig. 3). It may, however, well be that this presentation is, in fact, more common than the jaw lesion, since children

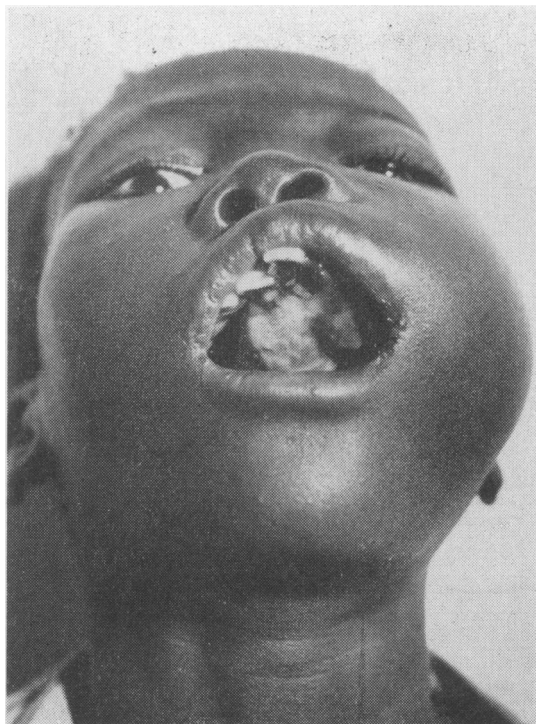


FIG. 2.—Tumour in the left maxilla in a boy aged eight years. Many of the teeth have fallen out.

with obviously malignant abdominal tumours are not usually transported long distances to hospital, and in the absence of autopsy evidence the tumours are less likely to be distinguished from other abdominal tumours. It should also be noted that, even though the jaw tumour has been the commonest presenting lesion, every patient subjected to laparotomy or coming to autopsy has been found to have one or more intra-abdominal tumours, located most frequently in the kidneys.

Clinically, the abdominal swelling is usually recognizable as:

- (a) A tumour mass in one or both loins.
- (b) An enlarged liver.
- (c) An epigastric tumour.
- (d) Bilateral ovarian tumours presenting as a freely mobile smooth mass in each iliac fossa.

Any of these may be present together.

The loin masses represent renal involvement, the commonest site of the tumour.

At autopsy the epigastric tumour has been found to consist of a large mass of neoplastic tissue in the coeliac region and believed to originate in lymph nodes.

The bilateral ovarian involvement is a character-

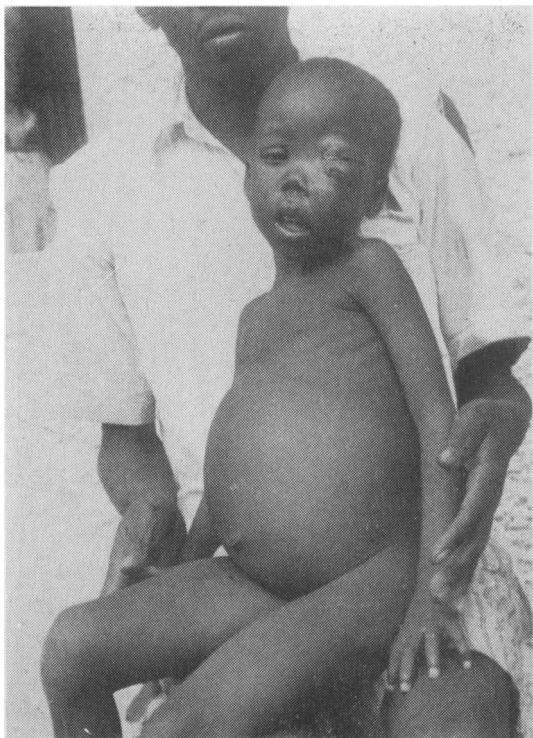


FIG. 3.—Large abdominal tumour accompanied by a left maxillary tumour involving the orbit in a boy aged six years.

istic and diagnostic feature. In the Cameroons attention has been drawn to this by Capponi (1953) and in Nigeria by Brew and Jackson (1961). Bilateral involvement of the ovaries has been found in nine of the 13 autopsies that have been performed on female patients at Mulago Hospital. Not infrequently the ovarian tumour has been the particular presenting lesion.

Paraplegia

Deposition of tumour within the extradural space in the spinal canal is, at least in Uganda, the commonest cause of paraplegia in children. It is easily distinguished from tuberculous paraplegia by the absence of clinical kyphosis or any obvious radiological change in the bone. The onset is rapid and is associated with double incontinence. In the majority of cases there is clinical evidence of tumour deposits in one or more of the other sites characteristic of this syndrome.

A Thyroid Tumour

Although this is rarely the lesion that brings the child to hospital, clinical bilateral involvement of the thyroid is common (Fig. 5).



FIG. 4.—Orbital tumour resembling an advanced retinoblastoma in a boy aged three years. Later a tumour of identical histological appearance developed in the neck. Clinically it appeared to originate in the left submandibular salivary gland, but no normal gland was found on section.

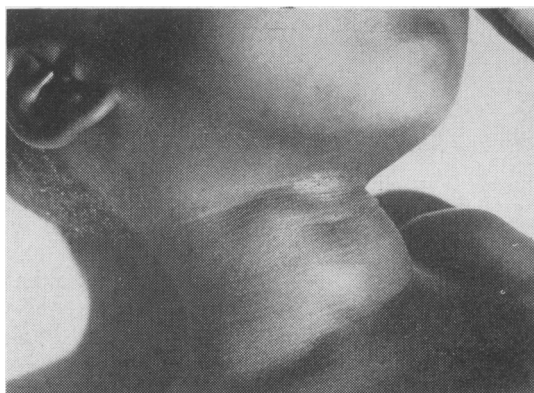


FIG. 5.—Tumour involving both lobes of the thyroid in a boy aged five years. There were also tumours in the left maxilla and in the upper abdomen.

A Salivary Gland Tumour

Despite the fact that the cervical lymph glands are rarely involved clinically, gross enlargement of the salivary glands is not uncommon. A tumour of the left sub-mandibular salivary gland has been seen to reach the size of a grapefruit (Fig. 6).

A Tumour in Long Bones

Relative to the very high incidence of jaw lesions, tumours in the rest of the skeleton are uncommon. They have, however, been observed in the femur (Fig. 7), tibia, humerus, clavicle, pelvis and cranium (one case only). In the long bones the tumours clinically resemble osteogenic sarcoma, but they occur at a younger age, grow even more

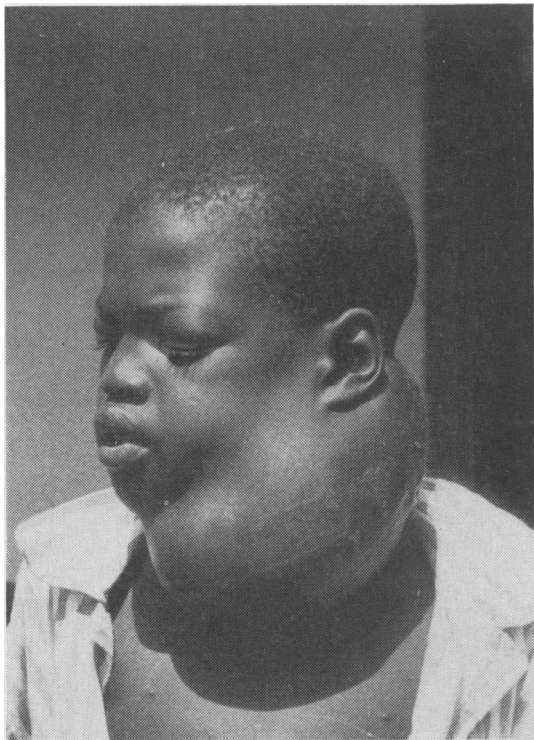


FIG. 6.—Tumour which originated in the left submandibular salivary gland in a boy aged eight years.

rapidly and are much less painful. Tumour has been observed to involve bone at either side of a joint without any demonstrable joint lesion. In all patients with lesions in the skeleton tumours have been observed in one or more of the other sites characteristic of this syndrome.

A Testicular Tumour

Tumours of the testis are not uncommon. All cases so far observed have been unilateral.

Involvement of the Breast

This has been seen in two patients.

Subcutaneous Lesions

These have been observed in two patients.

Radiological Features

The radiological appearances in the jaws and long bones are similar. The earliest change appears to be the development of multiple small areas of bone absorption, presumably representing multiple early tumour deposits. As the tumours grow these areas expand and coalesce, giving the appearance of massive bone absorption (Fig. 8). In the later stages of a jaw tumour the teeth lose

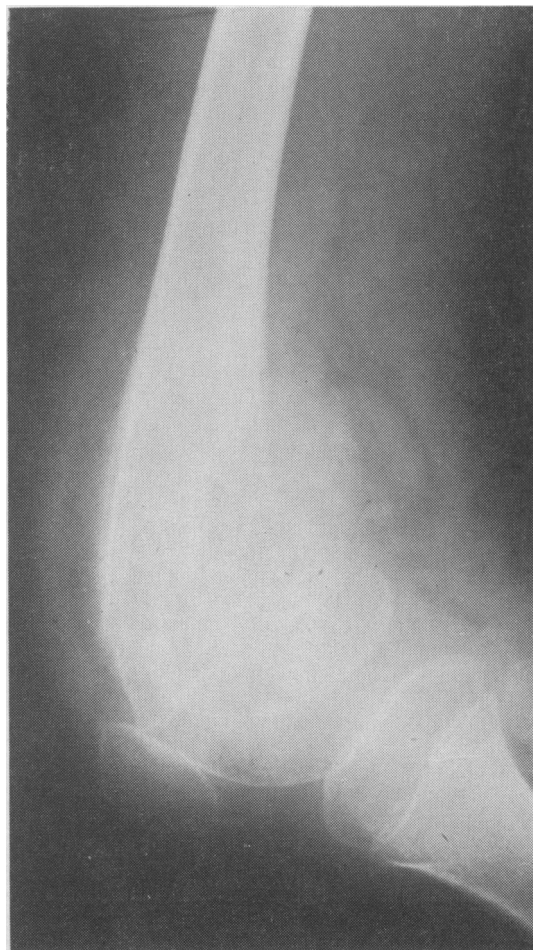


FIG. 7.—Radiograph showing tumour in the lower end of the right femur in a boy aged nine years. There was also a massive tumour protruding from the right orbit with destruction of the eye.

all attachment to bone and lie embedded only in the soft tumour tissue.

Course and Treatment

In no case has even temporary spontaneous remission been observed. Without therapy the majority of these children die within four months of the onset of symptoms. The rate of growth is illustrated in Fig. 9. Remission lasting over 14 months has been observed in two patients treated in the early stages with oral methotrexate. Radical removal of local lesions has been abandoned as quite unjustifiable in what is known to be a disseminated tumour. Similarly, perfusion therapy can be no more than locally palliative. In view, however, of the fact that the results of therapy

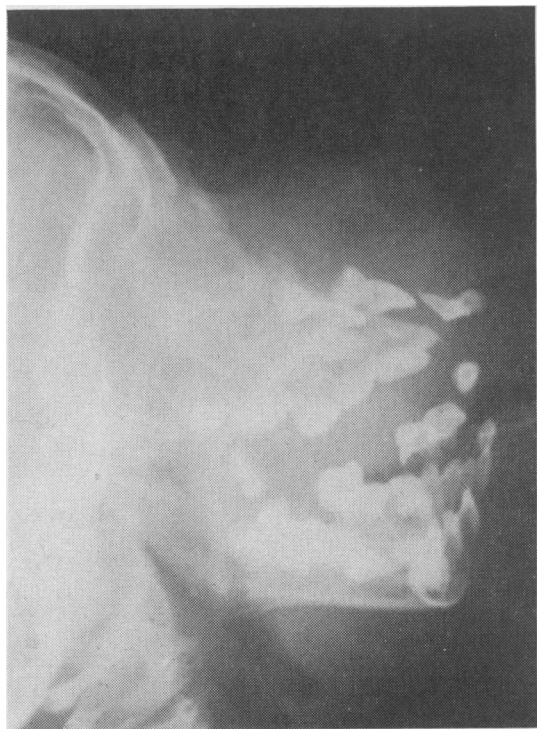


FIG. 8.—Radiograph showing tumour of the right maxilla and mandible in a boy aged five years. Displaced teeth are lying embedded only in soft tumour tissue. There was also a tumour above the left elbow without any radiological evidence of bone involvement.

appear to depend on the size of tumour mass, what Davies (1961) has referred to as 'bulk reduction surgery' is considered rational. In the jaw at least this does not involve mutilating procedures, as much of the very soft tumour can, in advanced cases, be virtually scooped out with a spoon.

Pathological Features

These have been described in detail by O'Connor and Davies (1960) and O'Connor (1961). In addition to the lesions described clinically, the organs and tissues most frequently found involved at autopsy have been the heart, the adrenals, the stomach and the small intestine. Although clinical enlargement of lymph nodes is rare, they are frequently found involved on histological examination. A detailed account of the tumour distribution has been given by O'Connor (1961). There is a strong tendency for bilateral organs to be bilaterally involved, as seen in the kidneys, adrenals, ovaries and thyroid.

Histology

This tumour has been identified by O'Connor and

Davies (1960) as a malignant lymphoma. O'Connor (1961) has described the histology in great detail and with profuse illustration. Although most cases conform to a definite histological pattern, variations appear from time to time. This has been ascribed to deviations in development from a very primitive mesenchymal cell.

Geographical Distribution

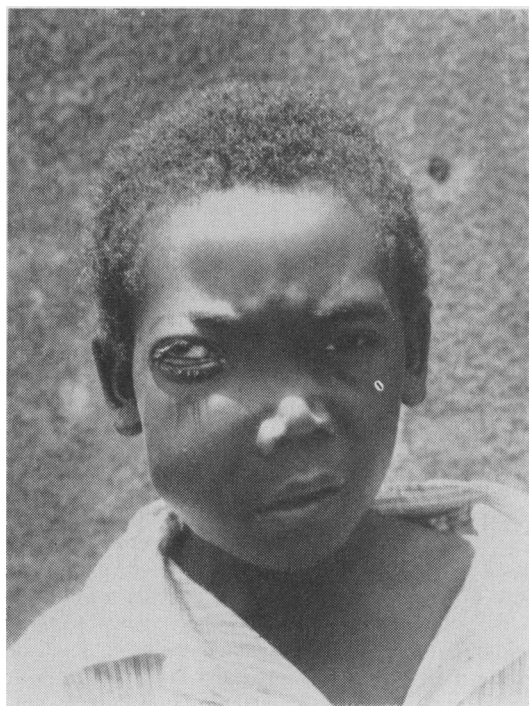
Perhaps the most significant feature of this unusual syndrome is that it is confined to certain distinct geographical areas (Fig. 10). It is recognized right across tropical Africa from the east to the west coasts, but it is unknown in the north or south. It has, as far as I am aware, not been recognized outside Africa, with the exception of New Guinea (van Seldam, 1961). It was at one time thought that an equatorial belt lay between certain lines of latitude, but further investigations have shown that this is not so. It is now apparent that in West and Central Africa the northern limit is about 15° latitude, but this level falls in the east. Along this northern limit tumour incidence drops as population density falls. The southern edge is much more significant, as tumour incidence falls off irrespective of population density. The tumour reaches the southern coast of West Africa and extends as far south as mid-Angola, though information from that country has been sparse. It appears to occur throughout the Congo and, with the exception of pockets which will be discussed later, it occurs throughout East Africa. Significantly, however, Zanzibar and Pemba are exempt. For the most part the Rhodesias are not affected, but Nyasaland and Mozambique are heavily involved. Thus there is seen to be a strip of coastal plain running down from the east edge of the tumour belt.

Within the belt there are areas where the tumour does not occur. These have yet to be defined, but it is known that the only part of Uganda exempt from tumour is the mountainous southwest, which is, incidentally, the most densely populated district in the whole country. Moreover, very few cases have been recorded from the relatively high country adjacent to the Ruwenzori Mountains in spite of considerable population density. It would thus appear that altitude is a limiting factor.

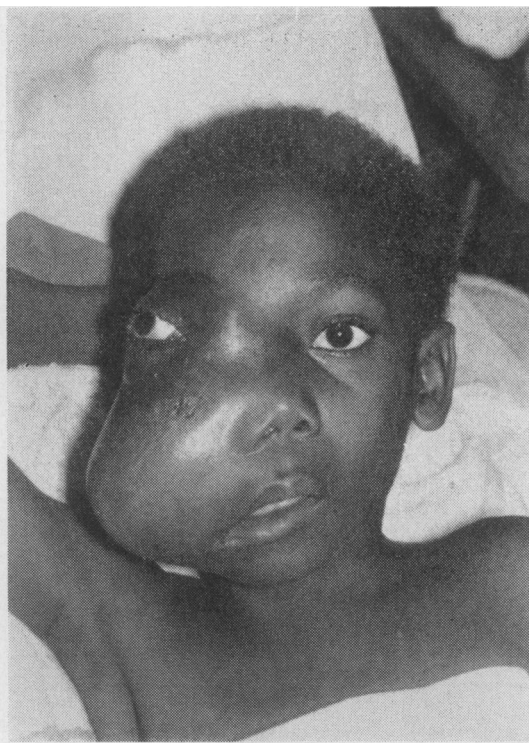
Although cases have been reported from hospitals in the Kenya Highlands, available evidence suggests that these cases have come from more low-lying country and have not been resident in the Highlands.

Discussion

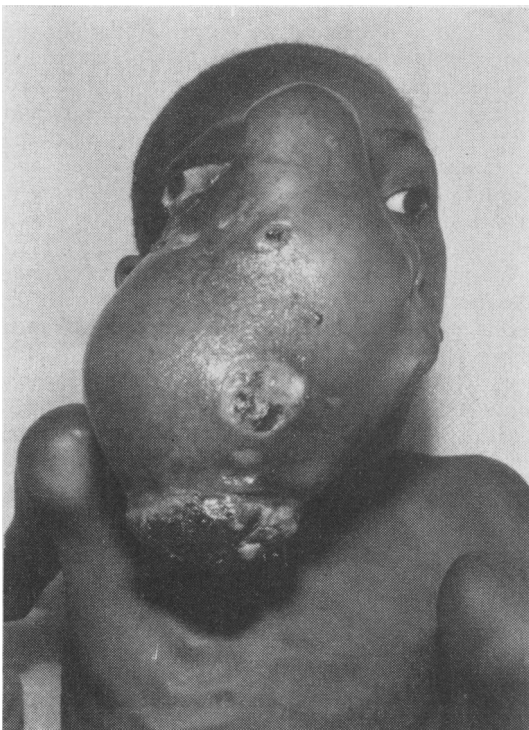
It may be wondered how this tumour syndrome



A



B



C

FIG. 9.—Tumour involving the right maxilla and right mandible in a boy aged eight years. This boy first reported with a tumour of the right maxilla associated with proptosis of the eye and a tumour of the right mandible. Under oral methotrexate therapy the mandibular tumour disappeared clinically and the maxillary tumour subsided considerably. Six months later the maxillary tumour failed to respond to therapy and grew rapidly. A. Condition September 13, 1960. B. Condition November 24, 1960. C. Condition January 18, 1961.

has passed unnoticed until the last few years. Individual trees had called for comment, but the wood had apparently not been seen. Rapidly growing tumours had been observed in the jaws of children, but had not been recognized as a specific entity and part of a multicentric tumour syndrome. Also the frequent occurrence of ovarian lymphosarcoma had been reported from the Cameroons (Capponi, 1953). It was the recognition that many unusual and hitherto unconnected tumours were, in fact, but different manifestations of one tumour syndrome that initiated investigation of the problem as a whole.

The most interesting aspects of this tumour syndrome are:

- (1) The characteristic anatomical distribution.
- (2) The limited geographical distribution.
- (3) The specific age incidence.

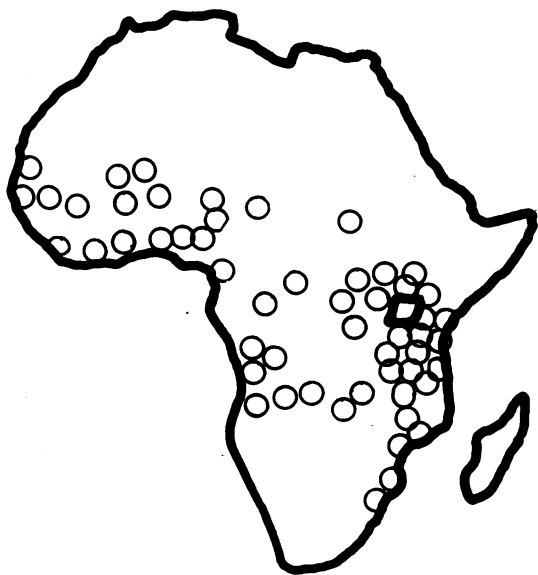


FIG. 10.—Map of Africa showing the known distribution of the syndrome. Each circle represents an area in which the tumour has been recognized. (With acknowledgment to the 'Annals of the Royal College of Surgeons of England'.)

The Anatomical Distribution

Although lymphomatous tumours are known to occur in all of the sites where they are characteristically found in this syndrome, the frequent simultaneous occurrence of tumours in a number

of these unusual situations has not hitherto been recorded. It is characteristic of this syndrome that not only are tumour deposits found in many widely separated organs simultaneously, but in the early stages of involvement of any single organ or structure the lesions are multiple before they coalesce to form one tumour mass. This is particularly evident in the kidneys, liver (Fig. 11) and bones (Fig. 7). The rarity of pulmonary lesions renders it unlikely that the tumours are secondaries from a metastasizing primary, and it is believed that the syndrome is produced by a multicentric tumour arising in many situations simultaneously. There is a striking similarity between the distribution of this tumour and the distribution of the experimentally produced polyoma. In both tumours deposits are found in the liver, salivary glands, breast and subcutaneous tissues, and the similarity between the bilateral multiple renal lesions found in both conditions is particularly striking. Moreover, in the Mill Hill polyoma Chesterman (1961) observed mesenchymal hyperplasia, presumably pre-cancerous, in the adrenals and ovaries, both of which organs are frequently involved in this malignant lymphoma syndrome. These similarities of distribution, in spite of dissimilar histological appearances, compel consideration of the possibility that the lymphoma syndrome may have a similar aetiology to the virus-induced polyoma. It was Professor Davies, at Makerere College, Kampala, who first drew attention to the possibility that virus infection might play a part in the causation of this tumour.



FIG. 11.—Multiple tumour deposits in the liver.

The Geographical Distribution

The limited geographical distribution lends further support to this speculation. Dr. Haddow (1961), Director of the East African Virus Research Institute, Entebbe, has pointed out that a map (Fig. 12) pattern similar to the known tumour distribution could be produced by eliminating certain areas from a map of Africa. These were:

- (a) Areas over 5,000 ft. and areas where seasonal mean temperature falls below 60°F., and
- (b) Areas with an annual rainfall of less than 20 in.

Altitude is, of course, related to temperature and rainfall to fauna. Both of these eliminating factors are known to be inimical to the existence of certain mosquitoes. The most striking similarity between the two maps is the tail running down the east coast, due, in the case of the climatic map, to the warm currents from the Indian Ocean turning south before reaching the African continent.

It is of significance to note that the tumour is not seen in the islands of Zanzibar and Pemba. In a district within the lymphoma belt on the main continent with a population equivalent to that of these islands at least four cases a year would be expected. But, in view of the fact that only a proportion of cases occurring in scattered communities reach hospital, and virtually all cases occurring in these thickly populated islands would be expected to seek medical attention, one might expect 10 or more cases to be recorded annually if the tumour existed with an incidence similar to that observed on the mainland. The tumour has not been recognized at all in spite of the fact that the surgeon in charge was familiar with these cases when working in Kenya. It can thus be assumed that the factors responsible for this tumour do not operate in these off-shore islands.

Still another interesting fact has recently come to light. Although the tumour is for the most part quite unknown in the Rhodesias, three cases have been seen by White (1961) in Bulawayo. At least one of his patients came from the Zambesi valley, and it may well be that conditions favourable to the development of malignant lymphoma exist in the Zambesi and Limpopo valleys, where temperatures do not reach the low levels recorded in the surrounding higher territory. If this could be substantiated it would add strong support to the theory of virus infection dependent on an arthropod vector.*

The Age Incidence

If the tumour were due to a virus infection, it could be postulated that, as in the case of polio-

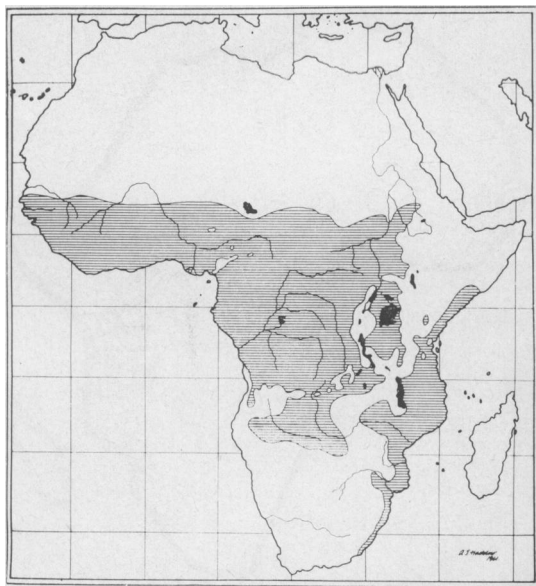


FIG. 12.—Map of Africa, in which the area left plain represents: (a) Areas over 5,000 ft. and areas where seasonal mean temperature may fall below 60° F. and (b) areas with less than 20 in. rainfall per year. (With acknowledgment to the 'Annals of the Royal College of Surgeons of England'.)

myelitis or experimental inoculation with diluted polyoma virus, only a fraction of those infected would produce the characteristic lesions of the lymphoma syndrome. Moreover, an inherited immunity could account for the virtual absence of cases in the first two years of life, as an acquired immunity would account for the rarity of the syndrome after puberty. Alternatively, a neonatal infection might result in tumour formation after a long incubation period. This would be in keeping with experimentally induced polyoma, which depends on very early inoculation.

Summary

The characteristic features of a tumour syndrome observed frequently in children in tropical Africa have been reviewed. The significance of these features as pointing to the possibility of a virus aetiology have been discussed. References have been given to sources where more detailed accounts of different aspects of this tumour can be found.

I wish to acknowledge my gratitude to the Department of Medical Illustration at Makerere College Medical School for Figs. 2, 7, 8, 10 and 12.

Figs. 10 and 12 are reproduced by kind permission of the 'Annals of the Royal College of Surgeons of England'.

I would particularly like to record my gratitude to my colleagues in the Surgical and Pathological Departments at Makerere College Medical School.

*A recent survey has confirmed that all cases recorded in the Rhodesias came from the river valleys.

REFERENCES

- BREW, D. ST. J., and JACKSON, J. G. (1961): Lymphosarcoma in the Ovary in Young African Girls in Nigeria, *Brit. J. Cancer*, **14**, 621.
- BURKITT, D. (1958): A Sarcoma Involving the Jaws in African Children, *Brit. J. Surg.*, **46**, 218.
- (1962): A Lymphoma Syndrome in African Children, *Ann. roy. Coll. Surg. Engl.* (in press).
- , and DAVIES, J. N. P. (1961): Lymphoma Syndrome in Uganda and Tropical Africa, *Med. Press*, **245**, 367.
- , and O'CONOR, G. T. (1961): Malignant Lymphoma in African Children: Part I. A Clinical Syndrome, *Cancer*, **14**, 258.
- CAMPBELL, A. C. P., GAINSFORD, W., PATERSON, E., and STEWARD, J. K. (1961): Tumours in Children, *Brit. med. J.*, **5224**, 448.
- CAPPONI, M. (1953): Note sur le cancer au Cameroun, *Bull. Soc. Ent.*, **46**, 605.
- CHESTERMAN, F. C. (1961): The Pathological Effects of the Mill Hill Polyoma Virus (M.H.P.), *Med. Press*, **245**, 350.
- DAVIES, J. N. P. (1961): Chemotherapy and 'Bulk Reduction' Surgery, *Brit. med. J.*, **i**, 1458.
- DAVIES, A. G. M., and DAVIES, J. N. P. (1960): Tumours of the Jaw in Uganda Africans, *Acta Un. int. Cancer*, **16**, 1320.
- HADDOW, A. (1961): Personal communication.
- O'CONOR, G. T. (1961): Malignant Lymphoma in African Children. Part 2. A Pathological Entity, *Cancer*, **14**, 270.
- , and DAVIES, J. N. P. (1960): Malignant Tumours in African Children, *Pediatrics*, **56**, 526.
- TEN SELDAM, R. E. J. (1960): Personal communication.
- WHITE, A. (1961): Personal communication.
- WILLIAMS, E. H. (1961): Personal communication.
-